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STUDY PROTOCOL

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Physiological and neurophysiological determinants of postcancer fatigue: design of a randomized controlled trial

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Abstract

Background: Postcancer fatigue is a frequently occurring, severe, and invalidating problem, impairing quality of life. Although it is possible to effectively treat postcancer fatigue with cognitive behaviour therapy, the nature of the underlying (neuro)physiology of postcancer fatigue remains unclear. Physiological aspects of fatigue include peripheral fatigue, originating in muscle or the neuromuscular junction; central fatigue, originating in nerves, spinal cord, and brain; and physical deconditioning, resulting from a decreased cardiopulmonary function. Studies on physiological aspects of postcancer fatigue mainly concentrate on deconditioning. Peripheral and central fatigue and brain morphology and function have been studied for patients with fatigue in the context of chronic fatigue syndrome and neuromuscular diseases and show several characteristic differences with healthy controls.

Methods/design: Fifty seven severely fatigued and 21 non-fatigued cancer survivors will be recruited from the Radboud University Nijmegen Medical Centre. Participants should have completed treatment of a malignant, solid tumour minimal one year earlier and should have no evidence of disease recurrence. Severely fatigued patients are randomly assigned to either the intervention condition (cognitive behaviour therapy) or the waiting list condition (start cognitive behaviour therapy after 6 months). All participants are assessed at baseline and the severely fatigued patients also after 6 months follow-up (at the end of cognitive behaviour therapy or waiting list). Primary outcome measures are fatigue severity, central and peripheral fatigue, brain morphology and function, and physical condition and activity.

Discussion: This study will be the first randomized controlled trial that characterizes (neuro)physiological factors of fatigue in disease-free cancer survivors and evaluates to which extent these factors can be influenced by cognitive behaviour therapy. The results of this study are not only essential for a theoretical understanding of this invalidating condition, but also for providing an objective biological marker for fatigue that could support the diagnosis and follow-up of treatment.

Trial registration: The study is registered at ClinicalTrials.gov (NCT01096641).

Keywords: Postcancer fatigue, Cognitive behaviour therapy, Peripheral fatigue, Central fatigue, Brain morphology, Brain metabolism, Physical condition, Physical activity

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Background

Postcancer fatigue

Postcancer fatigue (PCF) is a frequently occurring, severe, and invalidating problem in cancer survivors, impairing quality of life.[1,2] About 70 to 96% of the cancer patients undergoing chemotherapy and/or radiotherapy experience symptoms of fatigue.[3,4] The prevalence of PCF observed in longitudinal follow-up studies ranged from 19 to 39%.[1,5-8] Previous disease and treatment characteristics are unrelated to PCF.[2,4,9-12] However, there is some evidence that patients who are treated with only a surgery are less at risk for PCF[8] and survivors who are treated with more aggressive treatments are more at risk for PCF [1,13]. Cognitive behaviour therapy (CBT), especially designed for PCF, seemed to be an effective treatment option for PCF. [11,14] However, although it is now possible to effectively treat PCF, the nature of the underlying physiology of PCF remains unclear.

The term fatigue in the medical literature usually refers to fatigue experienced by the patient, but it can also refer to physiological fatigue. Fatigue experienced by the patient and its psychological aspects can be quantified using questionnaires. Physiological aspects of fatigue include peripheral fatigue, originating in muscle or the neuromuscular junction; central fatigue, originating in nerves, spinal cord, and brain; and physical deconditioning, resulting from a decreased cardiopulmonary function.

Peripheral and central fatigue

In physiology, fatigue is usually defined as the loss of voluntary force-producing capacity during exercise,[15] which can have a peripheral and a central origin.[16] During peripheral muscle fatigue, membrane excitability of muscle tissue is influenced due to a decrease in pH, accumulation of lactate, and changes in intra- and extracellular ion concentration.[17] Muscle fibre conduction velocity (MFCV), which can be determined by surface electromyography (sEMG), reflects the peripheral situation.[16] Alternatively, peripheral fatigue can be quantified by measuring the muscular force response to artificial electrical stimulation before and after exercise. Besides peripheral factors, a failure of drive from the central nervous system may also contribute to fatigue [18] This sub-maximal central activation during exercise, or central activation failure (CAF), is named central fatigue[16] and can be measured with a twitch interpolation technique.[19]

Physiological fatigue has been studied in patients with neuromuscular diseases,[20] in patients with chronic fatigue syndrome (CFS),[21] but also in cancer patients to evaluate cancer-related fatigue.[22] In a study of 16 cancer patients referred to palliative medicine and 16 matched non-cancer controls, neuromuscular testing

was applied to determine whether cancer-related fatigue is a more centrally or peripherally mediated disorder. [22] Patients suffering from cancer-related fatigue showed less peripheral muscle fatigue and more central muscle fatigue compared to their non-fatigued controls.

It should be noted that some psychological aspects of fatigue are different for different neuromuscular diseases [23] as well as for fatigue in CFS and for cancer-related fatigue. Nevertheless, CAF appears to be a shared neurophysiological feature of fatigue in all these diseases. Therefore, it is of great interest to know whether PCF is also characterized by CAF.

Although CAF implies a central origin of fatigue, it is still unclear from which part of the central nervous system the failure originates. Therefore, further studies on brain morphology and brain metabolism are essential to elucidate the (neuro)physiological basis of fatigue.

Brain morphology and metabolism

Using magnetic resonance imaging (MRI), several studies have reported structural abnormalities in the brains of patients with CFS. In a group of 259 fatigued patients, specific hyperintense small punctuated subcortical white-matter foci were observed.[24] Similar results have been reported by others.[25-27] Different research groups conducted voxel-based morphometry (VBM) in CFS patients and matched healthy controls and observed gray matter volume reductions in fatigued patients compared to non-fatigued controls.[28,29] Interestingly, it has been shown that CFS patients showed a significant increase in gray matter volume, localized in the lateral prefrontal cortex, after CBT.[30]

Magnetic resonance spectroscopy (MRS) provides a non-invasive window on metabolism in the brain. Studies with proton (^1H) MRS allow the detection and quantification of metabolites like choline, creatine, N-acetylaspartate, and lactate. Choline is a precursor of membrane phospholipids and an elevated choline level has been associated with increased cell membrane turnover, cell density, and gliosis. Choline levels vary over the brain and the choline to creatine ratio is higher in white matter than in gray matter. In a ^1H MRS study of the brain of CFS patients and eight age- and sex-matched healthy control subjects, the mean ratio of choline to creatine in the occipital cortex of fatigued patients was significantly higher compared to healthy controls.[31] The amount of creatine in the brain is assumed to be constant. An increased choline to creatine ratio suggests an abnormality of phospholipid metabolism and/or associated brain morphology. Similarly, in a ^1H MRS study of the left basal ganglia, a highly significant increase in the signal from choline-containing compounds was seen in CFS patients compared to age- and sex-matched healthy controls.[32] In three children with

CFS, ^1H MRS demonstrated a significantly higher choline to creatine ratio in the frontal cortex compared to healthy controls.[33] N-acetylaspartate is considered to be a marker of neuronal density and neuronal function. In one study, reduced levels of N-acetylaspartate were observed in the right hippocampus of seven CFS patients compared to healthy controls.[34] Elevated lactate in the brain may suggest cerebral energy dysfunction. The presence of elevated ventricular lactate was observed in sixteen CFS patients as compared to healthy controls.[35]

Especially for CFS, certain characteristics of brain morphology and metabolism may serve as objective biomarkers for fatigue. However, since CFS and PCF differ in some psychological aspects[36] it still needs to be shown that these characteristics also play a role in PCF.

Physical condition and activity

Despite the fact that current cancer treatments are increasingly efficacious for improving survival, they are toxic in numerous ways. Therefore, many cancer patients are forced to decrease their physical activity, possibly leading to physical deconditioning. Physical activity levels were significantly reduced after diagnosis in a study of 812 breast cancer patients.[37] It may be hypothesized that compared to non-fatigued cancer survivors, PCF patients have an impaired physical condition due to decreased physical activity after cancer treatment.

In a previous study comparing physical condition in a group of 20 CFS patients and 20 matched non-fatigued sedentary controls, physical condition did not significantly differ between both groups. Although as a clinical syndrome CFS and PCF show strong similarities, in PCF a clear precipitating moment can be identified that provoked fatigue, namely the diagnosis of cancer and its subsequent treatment. In contrast to PCF, not always a precipitating factor can be identified in CFS. Therefore, studies on physical condition, specifically in cancer survivors, are needed to investigate the physiology of PCF.

Methods/design

Study design

A randomized controlled trial (RCT) with 6 months follow-up will be conducted to identify and measure (neuro)physiological factors of fatigue in severely fatigued disease-free cancer survivors and to determine the role of these factors in the maintaining of fatigue. At baseline, fatigued and non-fatigued patients will undergo measurements for peripheral and central fatigue, brain morphology and metabolism, and physical condition and activity. Fatigued patients will be randomly assigned to either the intervention group, who will immediately start CBT, or the control group, who will start CBT after six

months. After six months follow-up, the measurements will be repeated in both groups of fatigued patients.

Ethical consideration

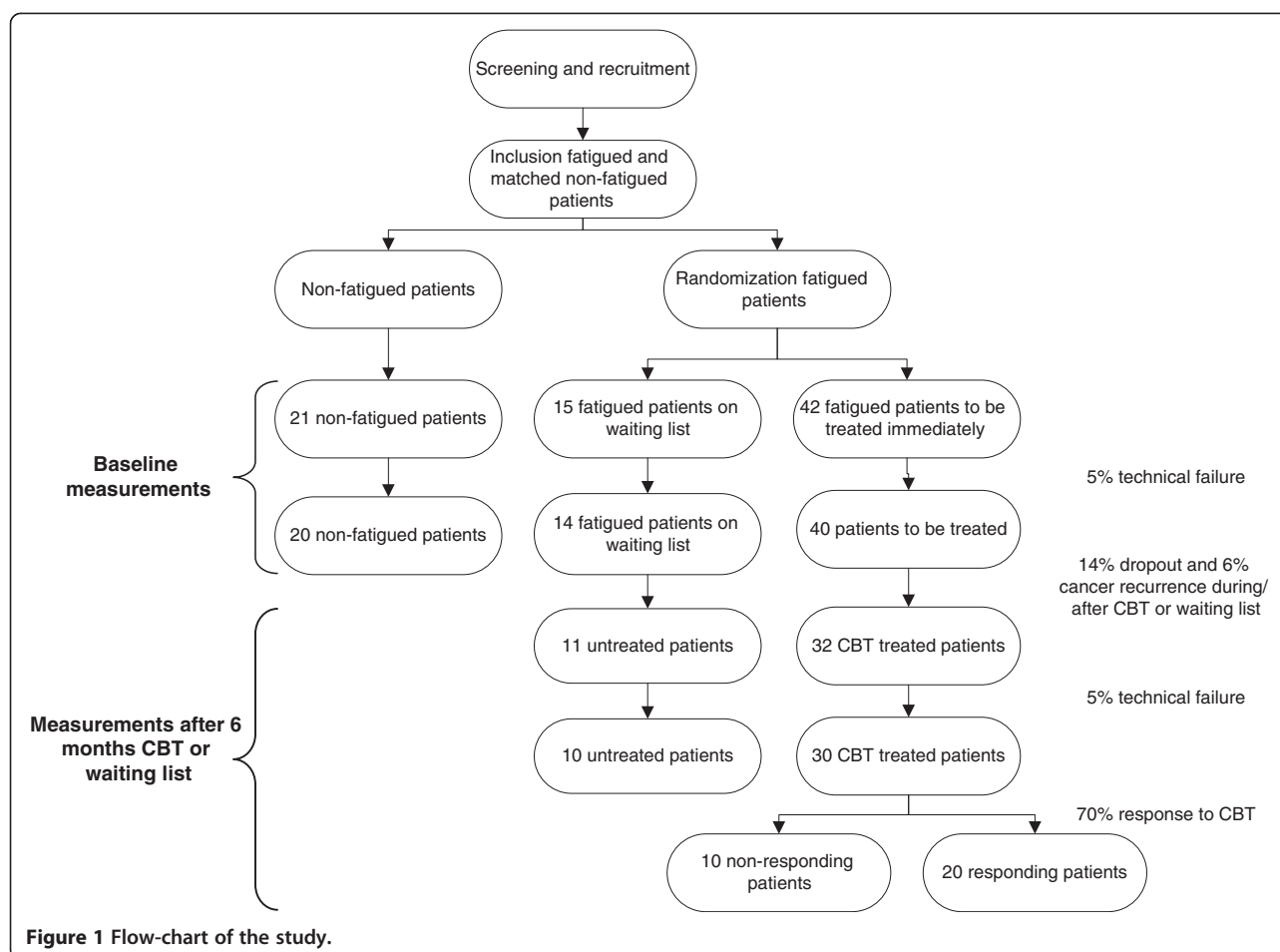
This study has been approved by the Medical Ethical Committee of the Radboud University Nijmegen Medical Centre (RUNMC). Patients will be informed about the study and informed consent will be obtained before randomization.

Study population

Patients who have been curatively treated for cancer and finished treatment at least one year before, will be asked by their physician to fill out the Checklist Individual Strength (CIS),[38] RAND-36,[39] Beck Depression Inventory for Primary Care (BDI-pc),[40] and some additional demographic and medical questions during their control-visits. Based on the scores of the fatigue severity subscale of the CIS (CIS-fatigue), patients with a cut-off score of ≥ 35 will be classified as severely fatigued. Severely fatigued patients, who are referred to the Expert Centre for Chronic Fatigue of the RUNMC and who met the in- and exclusion criteria of the study (Table 1), will be informed by their treating psychologist about the study. If the patients agree to be further informed about the study, the researcher will inform the patients extensively about the study and will ask for participation. Severely fatigued patients will be matched with non-fatigued patients with respect to age, sex, and previous cancer treatment (Figure 1). A total number of 57 severely fatigued and 21 non-fatigued cancer survivors will be included (see power calculation).

Table 1 Inclusion and exclusion criteria

Inclusion criteria	(1) Age between 19 and 65 years
	(2) Age at disease onset minimal 18 years
	(3) Treated for a malignant, solid tumour
	(4) Completion of treatment for cancer minimal 1 year ago (single treatment modality surgery/ current hormonal therapy permitted)
	(5) Disease-free, as defined by the absence of somatic disease activity parameters
Exclusion criteria	(1) Physical comorbidity that could explain the fatigue
	(2) Current psychological or psychiatric treatment
	(3) Brain tumour in the past
	(4) Contra-indication for MR examinations (e.g. claustrophobia)
	(5) Treatment with anti-depressive drugs, anti-epileptic drugs, or benzodiazepines
	(6) Insufficient command of the Dutch language to fill out questionnaires



Randomization and intervention

As shown in Figure 1, severely fatigued patients will be randomized to either the intervention group (75%) or the control group (25%). Randomization will take place per patient. Patients randomized to the intervention group will be treated with CBT for PCF, as described previously.[14] The treatment consists of 12–14 individual sessions in six months. Patients randomized to the control group will be treated with CBT after six months.

Outcome measures

Peripheral and central fatigue

To obtain maximal voluntary contraction (MVC) of the biceps brachii muscle, participants will make MVCs, with 1 min intervals, until no further force increase was observed. After a rest period of 10 min, peripheral and central fatigue will be measured during a 2 min sustained MVC of the biceps brachii muscle.[18] During these 2 min, electrical endplate stimulation over the motor points of the medial and lateral head of the biceps brachii muscle will be applied every 15 s, leading to superimposed force responses. Patients will be verbally

encouraged to perform maximally throughout the 2 min. An indicator of peripheral muscle fatigue is MFCV, which will be measured using sEMG.[16] Peripheral muscle fatigue will also be quantified by measuring the muscular force response to electrical endplate stimulation before and after the test. An indicator of central muscle fatigue is additional force production upon electrical endplate stimulation during exercise.[18] Submaximal central activation during exercise, or CAF, will be measured using a twitch interpolation technique.[19]

Brain morphology and metabolism

Global volumes of gray and white matter, subcortical brain volumes, and brain metabolite concentrations will be obtained. MR measurements will be performed on a 3 Tesla MR System using a radiofrequency head coil. High resolution (1 mm³), T1 weighted MR images of the whole brain will be acquired using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence. Normalizing, bias-correcting, and segmenting into global volumes of gray and white matter will be performed using the VBM method.[41] Automatic

segmentation of subcortical brain structures was performed using the FIRST module of FSL.[42]

^1H MR spectroscopic imaging (MRSI) will be performed, with special interest for the hippocampus, the occipital cortex, the frontal cortex, and the ventricles. The ^1H MRSI will allow the identification and quantification of metabolites like choline, creatine, N-acetylaspartate, and lactate. Volume selection will be performed with a semi-localized by adiabatic selective refocusing (semi-LASER) pulse sequence [43] with a repetition time of 1500 ms, an echo time of 30 or 136 ms, and a voxel size of 10 mm^3 . The data will be analyzed using LCModel software.

Physical condition and activity

To measure maximal oxygen consumption (VO_2max) a maximal exercise test will be performed.[44] In addition to the determination of VO_2max , carbon dioxide production, heart rate, respiratory quotient, and ventilation will be measured. Patients will cycle with an increased workload of 10 Watt/min for women and 20 Watt/min for men. Patients will be verbally encouraged to perform maximally until exhaustion.

Daily activity will be measured during two weeks using an actometer.[45] The actometer used is a motion-sensing device, worn around the ankle, which can register and quantify human physical activity. The actometer has a piezoelectric sensor that is sensitive in three directions. Accelerations of the built-in sensor larger than a predefined threshold are considered as activity and are stored in an internal memory every five minutes. A general physical activity score expressed in the average number of accelerations per 5-min period will be provided for the whole measurement period. Actometer testing is part of the standard care if patients are referred for CBT. To assess the effect of the maximal exercise test on the daily activity of patients, they will wear an actometer for an additional five days after the maximal exercise test.

Finally, participants will score their physical activity level long before cancer diagnosis on a 10 point numeric rating scale.

Fatigue and psychosocial measures

Fatigued severity will be measured using the CIS-fatigue (8 items, 7-points Likert Scale, severity range from 8 to 56).[38] High scores indicate a high level of fatigue. This questionnaire has excellent psychometric properties, including good reliability and discriminative validity.[46] Simultaneously to the actometer measurements, daily observed fatigue (DOF) will be measured with the Self-Observation List (4 times a day, 4-point scale)[47] two weeks prior and five days subsequent to the maximal exercise test. This instrument gives the actual level of daily fatigue. In this way, the relation between actual fatigue

levels and the (neuro)physiological measures can be accessed directly.

To examine whether self-efficacy (SE) regarding the maximal exercise test could be an explanation for possible discrepancies in VO_2max between fatigued and non-fatigued participants, SE regarding the maximal exercise test will be measured using a task-specific SE questionnaire. This questionnaire consists of 9 questions concerning sense of control (each item scored on a 4 point numeric scale, total score range from 9 to 36) and was adapted from the self-efficacy scale (SES)[48] The SES measures the perceived level of control over fatigue, whereas the task-specific SE questionnaire used in this study measures the sense of control regarding the test. A higher score indicates a higher sense of control regarding the maximal exercise test.

To assess whether environmental factors, like social support (SS) for exercise, may influence physical activity behaviour, SS will be investigated using the shortened van Sonderen SS Inventory (SSL).[49] The SSL is divided into the SSL-I (amount of SS, 8 questions, score range from 8 to 32), the SSL-D (discrepancy between the amount of SS and the desired amount of SS, 8 questions, score range from 0 to 32), and the SSL-N (negative interactions, unsupportive behaviour, 7 questions, score range from 7 to 28). A higher score indicates a higher amount of SS, discrepancy, or negative interactions.

Statistical analysis

Independent samples t tests will be performed testing baseline differences in primary and secondary outcome measures between fatigued and non-fatigued cancer survivors. Baseline differences between the therapy and waiting list condition are entered as covariates in further analyses. A paired t test will be performed to test whether differences can be observed within the therapy or waiting list condition from baseline to follow-up. Differences between the therapy and waiting list group on the change in outcome measures from baseline to 6 months later will be calculated with analyses of covariance (ANCOVA).

Power calculation

From previous studies in patients with CFS compared to healthy controls we know that groups of at least 10, preferably 20 patients per condition are sufficient to detect significant differences in (neuro)physiological parameters measured with sEMG, MRI, and exercise testing. [21,28,50,51] To identify (neuro)physiological characteristics of fatigue, a comparison of baseline measurements with an age, sex, and previous cancer treatment matched group of 20 non-fatigued patients is sufficient. Fifty seven severely fatigued patients are needed to measure a change in (neuro)physiological factors due to CBT. As

depicted in Figure 1, we assume that 5% of the measurements will yield technically insufficient data and 20% of the fatigued patients will drop-out from the study (14% drop-out due to failure to complete CBT or the follow-up measurements and 6% due to cancer recurrence during or after CBT or waiting list). Assuming that about two third of the patients who complete CBT will have a clinically significant response to CBT, defined as a CIS-fatigue score of less than 35 points, there will be 20 responding patients, 10 non-responding patients, and 10 untreated patients. Based on 30 patients in the CBT condition and 10 patients in the waiting list condition and assuming that the success rate of CBT is about 67% and the chance to recover spontaneously in the waiting list condition is maximally 10%, the power of the study to demonstrate a significantly greater decrease in CIS-fatigue score in patients in the intervention condition than in patients in the waiting list condition will be at least 80%.

Discussion

To the best of our knowledge, this will be the first study that characterizes (neuro)physiological factors of fatigue in disease-free cancer survivors and the changes of these factors in a randomized controlled way.

Studies on physiological aspects of PCF mainly concentrate on (cardiopulmonary) deconditioning. Other aspects of fatigue, like peripheral and central fatigue and brain morphology and function have been studied for patients with fatigue in the context of CFS and neuromuscular diseases and show several characteristic differences with healthy controls. CAF appears to be a shared neurophysiological feature of fatigue. CFS patients showed a significant reduced gray matter volume compared to healthy controls and even showed a significant increase in gray matter volume after CBT. Altered levels of specific metabolites in the brains of patients with CFS, measured with ^1H MRS, have been reported. CFS patients showed a significant reduced physical activity, measured by actigraphy, compared to healthy controls. Therefore, further studies on (neuro)physiological aspects of fatigue in cancer survivors are essential not only for a theoretical understanding of this invalidating condition, but also for providing an objective biological marker that could support the diagnosis of fatigue and follow-up of the treatment of fatigue.

In conclusion, the aim of this study is to identify and measure physiological, structural, and metabolic factors of fatigue in disease-free cancer survivors and to determine the role of these factors in the maintaining of fatigue. The identification of (neuro)physiological factors of persistent fatigue can help to improve the diagnostics of fatigue, predict therapy outcome, and facilitate other treatment options. Finally, if (neuro)physiological

characteristics of fatigue can be influenced by CBT, it will enhance our understanding of the mechanism causing fatigue.

Abbreviations

ANCOVA: Analyses of covariance; BDI-pc: Beck depression inventory for primary care; CAF: Central activation failure; CBT: Cognitive behaviour therapy; CFS: Chronic fatigue syndrome; CIS: Checklist individual strength; CIS-fatigue: Fatigue severity subscale of the checklist individual strength; DOF: Daily observed fatigue; ^1H : Proton; MFCV: Muscle fibre conduction velocity; MPRAGE: Magnetization prepared rapid acquisition gradient echo; MRI: Magnetic resonance imaging; MRS: Magnetic resonance spectroscopy; MRSI: Magnetic resonance spectroscopic imaging; MVC: Maximal voluntary contraction; PCF: Postcancer fatigue; RCT: Randomized controlled trial; RUNMC: Radboud University Nijmegen Medical Centre; sEMG: Surface electromyography; SES: Self-efficacy scale; SS: Social support; SSL: Social support inventory; SSL-I: Amount of social support; SSL-N: Negative interactions of social support; SSL-D: Discrepancy in social support; VBM: Voxel-based morphometry; semi-LASER: semi-localized by adiabatic selective refocusing; SE: self-efficacy.

Competing interests

The corresponding author and the co-authors have no conflicts of interest to declare.

Acknowledgements

This work is supported by the Dutch Cancer Society [KUN 2008–4002].

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Authors' contributions

HP is primary investigator and is responsible for patient recruitment, data collection, data analysis, and drafting the manuscript. HL, GB, MZ, and AH designed the study and obtained funding. HL, GB, MZ, MH, and AH supervised the study. All authors read and approved the final manuscript.

Received: 9 May 2012 Accepted: 18 June 2012

Published: 18 June 2012

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doi:10.1186/1471-2407-12-256

Cite this article as: Prinsen et al.: Physiological and neurophysiological determinants of postcancer fatigue: design of a randomized controlled trial. *BMC Cancer* 2012 **12**:256.